

REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-22, 24-50, and 58 are pending with entry of this response. Claim 58 is added herein to present additional clarifying embodiments of the invention and adds no new matter to the application as filed. For example, it is supported by the originally filed claims. Applicant therefore respectfully requests that the new claim be entered.

35 U.S.C. §103(a)

The independent claims were rejected under 35 U.S.C. §103(a) as allegedly obvious over Dooley, in view of Lockhart and Porkka. The Examiner also rejected dependent claims under 35 U.S.C. §103(a) over Dooley and further in view of various combinations of Lockhart, Porkka, Cho, Nilsen, and Shuber. Applicant respectfully traverses.

A finding of obviousness requires a determination of whether “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 USC § 103(a). As the Federal Circuit has repeatedly indicated, this inquiry ultimately involves determining “whether a person of ordinary skill would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been a reasonable expectation of success in doing so.” *Dystar Textilfarben GmbH v. C.H. Patrick Co.* 80 USPQ2d 1641 at 1645 (Fed. Cir. 2006). The determination of the questions of motivation and expectation of success are based upon a four part factual inquiry:

- (1) the scope and content of the prior art;
- (2) the differences between the claimed invention and the prior art;
- (3) the level of ordinary skill in the art; and,
- (4) consideration of secondary indicia of non-obviousness.

Dystar, id, quoting *Graham v. John Deere Co.*, 383 US 1, 17 [148 USPQ 459] (S. Ct. 1966). The Supreme Court recently reaffirmed the factual analysis established in *Graham v. John Deere Co.*, cautioning that the question of motivation to combine the prior art must be approached with “common sense,” rather than as a rigid formula:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR International Co. V. Teleflex inc. et al. 550 U. S. ____ (2007) slip opinion page 6.

The scope and content of the prior art

The combination of references does not render the claimed invention obvious. The combination of references (A) entirely fail to teach the elements of the claim; and (B) no specific “common sense” motivation exists in the prior art for the combination. In addition, as will be discussed in considering the differences between the prior art and the invention and the level of skill in the art, no expectation of success in the proposed combination, derived from the prior art, can possibly be made out for the proposed combination. Complete consideration of the Graham factors and the legal standards of motivation and expectation of success clearly establish the *non-obvious* nature of the invention.

The Elements Of The Claim Are Not Taught In The Combination Of References

In considering the scope and content of the prior art, a first basic requirement for establishing obviousness is that the combination of references must actually teach all of the elements of the claims. MPEP 2143.03. The combination of references in the rejection entirely fails to meet this most basic of factual requirements for establishing obviousness.

The references, when considered individually or together, fail to teach a main element of the claimed invention, e.g., the ability to analyze gene expression for multiple samples on a single array. As claimed, each sample on the array represents a different biological sample and contains a plurality of nucleic acid species, which are detected with a

set of probes comprising different detectable labels. These probes allow the identification of the different nucleic acid species in each sample.

For example, it is explicitly stated in step (c) of the claimed methods that each nucleic acid sample comprises a plurality of different nucleic acid species and in step (e) that each probe comprises a different detectable label. The nucleic acids that are used in any of the cited art to construct the arrays are single nucleic acid species at each addressable location on the array. Therefore, the references do not teach every element of the claimed invention, nor does the rejection even allege that these elements are taught in the prior art.

No Specific Motivation for the Combination Exists

The Federal Circuit has articulated a subsidiary factor to be considered when evaluating the scope and content of the prior art, i.e., whether the combination of references is motivated by the prior art, and not simply by Applicants disclosure. *Dystar Textilfarben GmbH v. C.H. Patrick Co.* 80 USPQ2d 1641 at 1645 (Fed. Cir. 2006), quoting *Graham v. John Deere Co.* 383 U.S. at 36.

Even if many of the individual elements of the claims could be found in the prior art as well as the desire to analyze more compounds faster and more efficiently, the art must contain some suggestion or motivation to combine these elements in the manner claimed. The universe of possibilities is huge regarding possible changes to array technology and some suggestion must be presented as to why one of skill would have selected this combination from all the possible elements.

The Office alleged that one of skill would be motivated by cost-effectiveness to use the informative array of Dooley with the array method of Porkka, e.g., the immobilization of genes to be identified on the array. The Office alleged that this would be advantageous to one of skill in the art because it would reduce the number of gene sequences on the array. While it may be true that one of skill in the art would be motivated by cost-effectiveness to decrease the number of genes on the array, the claimed invention provides a different alternative than the one arrived at by a combination of Dooley and Porkka, e.g., depositing multiple nucleic acids at each spot on the array.

If one's motivation to combine the two references is to increase the throughput of compound screening, then one would not achieve very much since Porkka only

teaches screening of one biological sample per array. Although it is asserted that Porkka flips the array, it still puts only one nucleic acid species on each spot on the array. The array format of Porkka, even if reversed, does not provide the same benefit as the claimed invention. Because no great advantage would ensue from the combination of Dooley and Porkka, there would be no motivation to combine them. Therefore, because the combination of Dooley and Porkka does not provide the same advantages as the claimed invention, the question of motivation becomes moot.

The differences between the claimed invention and the prior art

The second Graham factor relates to the differences between the claimed invention and the prior art. In this case, the differences are significant enough that a rejection for obviousness cannot be upheld.

The claimed invention relies on the use of a plurality of nucleic acid species at a single array address to analyze multiple genes simultaneously in multiple samples, e.g., each nucleic acid sample represents the total expressed RNA from a single biological sample. The prior art arrays a single nucleic acid species at each address, e.g., the entire array is used to analyze the expression products of a single sample. Therefore, the claimed invention achieves a level of throughput and efficiency not even hinted at in the prior art. For example, in Porkka, 1536 clones from a single sample being analyzed on a single array would be considered an achievement. *See, e.g.*, Porkka, page 78, last paragraph. The claimed invention allows several genes from each of a plurality of samples, e.g., 1536 different samples, to be analyzed simultaneously on a single array.

This difference is further illustrated by Figure 2 in Porkka, in which two arrays are used to analyze the expression products of two samples; each sample's expression products are deposited onto a separate array, e.g., with a different spatial location for each expressed gene. The results for two different tissue samples in Porkka require two arrays as shown in Figure 2, e.g., Figure 2A provides the results for benign prostatic hyperplasia tissue (BPH) and Figure 2B for the prostate cancer cell line (PC-3).

In the claimed invention, these two samples could each be deposited onto a different addressable location on the same array, with all of the expression products for each

sample represented on one spot on the array. With the differentially labeled probes, the claimed invention allows an increase in throughput not even remotely hinted at in the prior art, e.g., the ability to test multiple samples simultaneously for a plurality of genes. The claimed methods use a probe set not taught in the prior art as well as samples comprising multiple nucleic acid species that are also not present in the prior art.

Neither an individual reference nor the combination of references cited in the rejection provide the level of multiplexing provided by the claimed methods. The set of probes and the method of arraying the expression products of a plurality of samples are different from those presented in the prior art or any combination of prior art presented in the Action.

The level of skill in the art

While the level of skill in the prior art is quite extensive, the idea of arraying multiple nucleic acid species at a single address in the reversed array format as claimed was non-existent in the art.

No Expectation of Success Existed at the Time of the Invention for the Proposed Combination

Applicant does not dispute that arrays are taught in the prior art or that a need for higher throughput, e.g., for drug discovery or design is desirable. However, the fact that arrays are known and that increasing the number of genes and/or the number of samples that can be analyzed simultaneously is desirable, does not constitute sufficient motivation to combine the specific prior art references cited nor any expectation that such a combination would work. In fact, one reason it would not work is that every element of the claimed method is not present in the prior art and there is no suggestion in the prior art for the particular combination as claimed.

The claimed invention uses a non-traditional microarray configuration, where the normal sample/probe relationship is inverted. In this novel configuration, a plurality of nucleic acid samples corresponding to expressed RNA samples are affixed onto an array (e.g., a solid phase support surface). This array is then probed (*i.e.*, used in a hybridization reaction) with a plurality of soluble phase probes of defined sequence, wherein each probe

comprises a distinct label. In addition to the reversed format of the array, each of the samples on the array comprises a plurality of nucleic acid species, wherein each plurality is representative of the expression products of a different biological sample.

The array format in Porkka, although it may be reversed, does not work as the claimed invention does because it does not deposit multiple nucleic acid species on a single addressable location of the array and then probe the array with a set of probes comprising different detectable labels. Therefore, even if one were motivated to combine the two references, one would not have much expectation of success regarding increased throughput with the methods of Porkka and Dooley combined. The claimed invention allows a vast increase in throughput over the art, individually or combined.

Furthermore, the addition of the teachings of Cho (*PNAS*, 2001, 98(17):9819-9823), Nilsen (USPN 6,046,038), and/or Shuber (USPN 5,882,856) to the teachings of Dooley, Lockhart, and Parkka fails to remedy the deficiencies detailed above. Thus, even with their additional teachings, the current invention is not obvious. For example, because the combination of Cho, Nilsen, and/or Shuber with Dooley, Lockhart, and Parkka fails to teach all elements of the independent claims, the addition of any purported teachings from Cho, Nilsen, and/or Shuber is moot in regard to the dependent claims.

In conclusion, the prior art does not teach every element of the claimed invention and therefore any motivation to combine the references is moot and any expectation of success for the combination of references is inapplicable because it would result in an entirely different method than that claimed. Upon consideration of the Graham factors, it is clear that the differences between the prior art and the claimed invention are too great to support a rejection based on obviousness. In view of the arguments above, Applicant asserts that the claims are non-obvious and respectfully request that the rejection be withdrawn.

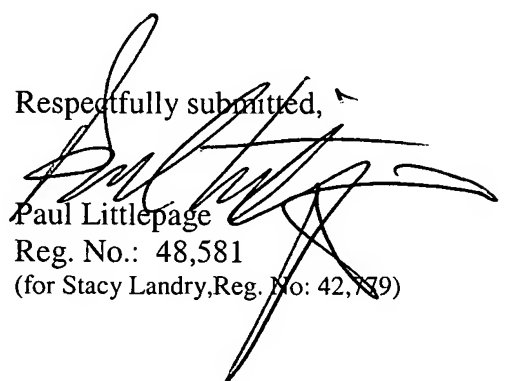
Appl. No. 10/622,010
Amdt. Dated January 2, 2008
Reply to Office action of July 2, 2007.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this application are in condition for allowance. If the Examiner believes there are any remaining issues regarding the patentability of the pending claims, the Examiner is encouraged to contact the undersigned by telephone to expedite the issuance of a Notice of Allowance.

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Respectfully submitted,



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Attachments:

- 1) A petition to extend the period of response for 3 months;
- 2) A transmittal sheet;
- 3) A fee transmittal sheet;
- 4) A receipt indication postcard.